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The relationship between generalized anxiety disorder, depression and mortality in old age

Tjalling J. Holwerda[1,2]*, Robert A. Schoevers[1,2], Jack Dekker[1], Dorly J. H. Deeg[2], Cees Jonker[2] and Aartjan T. F. Beekman[2]

[1]*Department of Psychiatry, Mentrum Mental Health Care, Amsterdam, The Netherlands*
[2]*Department of Psychiatry, Vrije Universiteit Medisch Centrum, Amsterdam, The Netherlands*

SUMMARY

Background The association between depression and an increased risk of death in elderly persons has been established in both clinical and community studies. Co-occurrence of depression and generalized anxiety has been shown to represent more severe and more chronic psychopathology. However, little is known about the relation between generalized anxiety disorder, mixed anxiety-depression (generalized anxiety disorder and depression) and excess mortality in the elderly.
Objective To investigate whether generalized anxiety and mixed anxiety-depression are associated with mortality.
Method Generalized anxiety disorder, mixed anxiety-depression and depression were assessed in 4051 older persons with a ten-year follow-up of community death registers. The mortality risk of generalized anxiety, depression and mixed anxiety-depression was calculated after adjustment for demographic variables, physical illness, functional disabilities and social vulnerability.
Results In generalized anxiety disorder and mixed anxiety-depression no significant excess mortality was found. In depression a significant excess mortality was found in men [HR 1.44 (1.09–1.89)] but not in women [HR 1.04 (0.87–1.24)] after adjustment for the different variables.
Conclusions In elderly persons depression increases the risk of death in men. Neither generalized anxiety nor mixed anxiety-depression are associated with excess mortality. Generalized anxiety disorder may even predict less mortality in depressive elderly people. The relation between generalized anxiety disorder and its possibly protective effect on mortality has to be further explored. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — generalized anxiety disorder; depression; mortality

INTRODUCTION

The association between depression and an increased risk of death has been firmly established in both clinical and community studies, in some studies this association was stronger in men (Penninx *et al*., 1999; Schoevers *et al*., 2000; Blazer *et al*., 2001; Cuijpers and Smit, 2002). Compared to studies in depression, studies on the relation between anxiety and mortality are sparse. Findings are frequently inconsistent because of sample differences in co-morbid conditions, socio-economic status and unhealthy lifestyles, which are not controlled for. In a large study among older persons it was found that, adjusted for lifestyle variables, demographic characteristics, functional limitations, cognitive functioning and chronic physical disease, men with anxiety had a mortality risk of 1.78 (1.01–3.13) while in women no relationship was found. In this study four anxiety disorders were included: phobic, panic, generalized anxiety and obsessive–compulsive disorder (Van Hout *et al*., 2004). However, no mortality data were reported on specific anxiety disorders. A general population study showed that depression but not generalized anxiety is associated with an increased risk of death (Murphy *et al*., 1987). In a large study of 5057 patients referred to a cardiology department for routine exercise testing, in which survival data were obtained after five years, it

*Correspondence to: T. J. Holwerda, LASAEMGO, Vrije Universiteit Medical Centre, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands. E-mail: tjalling.holwerda@mentrum.nl

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was found that symptoms of anxiety and depression had different predictive effects on mortality. It was found that, when controlling for physical risks, anxiety was associated with a lower mortality risk and depression with a higher mortality risk (Hermann *et al*., 2000).

Investigating the relation between (generalized) anxiety and/or depression and excess mortality is complicated by the fact that the presence of (generalized) anxiety is significantly associated with depression. Onset and offset of (generalized) anxiety and depression frequently occur at the same time and recovery rates of (generalized) anxiety and depression are also related (Castillo *et al*., 1995; Åström, 1996; Livingston *et al*., 1997; Beekman *et al*., 2000). In the group of anxiety disorders it is suggested that generalized anxiety disorder in particular may lie on a continuum with depression. It may be that the diagnostic categories depression, generalized anxiety and mixed anxiety depression may represent the same disorder at a different level of severity or at a different stage of development (Liebowitz *et al*., 1990; Schoevers *et al*., 2005). In comparison with either depression or generalized anxiety, the co-occurrence of depression and generalized anxiety represents more severe and more chronic psychopathology. Moreover, remission rates for depression and co-existing generalized anxiety are lower in comparison with 'pure' depression or 'pure' generalized anxiety disorder. Generalized anxiety often progresses to depression or depression with generalized anxiety disorder, suggesting a pattern of temporal sequencing (Schoevers *et al*., 2003; Schoevers *et al*., 2005). However, it has also been suggested that, although high levels of co-morbidity between depressive disorders and anxiety disorders have been found, anxiety disorders and depressive disorders merit separate study because risk factors reveal more differences than similarities (Beekman *et al*., 2000). Also was found that generalized anxiety disorder and major depressive disorder tend to have a different onset and remission of the disorders. This further supports the distinction of late life generalized anxiety from major depressive disorder (Lenze *et al*., 2005). Finally different neurobiological mechanisms in generalized anxiety and depression indicate a biological distinction between generalized anxiety and depression (Nutt, 2001).

On the basis of these observations we were interested in investigating the relation between generalized anxiety, depression and excess mortality. The main objectives of our study were to:

1. assess whether generalized anxiety disorder is associated with excess mortality in older persons in the community;
2. assess whether this association, if present, is modified by co-morbid depression and;
3. assess whether this association, if present, is modified by sex and other explanatory and confounding factors.

METHODS

Sample and non-response

The Amsterdam Study of the Elderly (AMSTEL) is a longitudinal study of a large and representative sample of non-institutionalised community living older persons on mental health problems, medical diagnoses and demographic characteristics. The sampling and data collection procedures have been described elsewhere (Launer *et al*., 1993; Schoevers *et al*., 2000, 2003). In short, the lists of 30 general practices were used as a sampling frame. Within each practice respondents were randomly selected from four age strata spanning five years each (65–69 to 80–84). The population base for AMSTEL included almost all the non-institutional individuals in the age bracket of 65–84 who lived in the city of Amsterdam. The study sample corresponded to the Amsterdam population in terms of age and gender. An age-stratified sample was drawn. Four thousand and fifty-one subjects (71.5%) responded, gave informed consent and were interviewed at baseline. Non-response in the younger old (<75) was associated with poor performance on cognitive tests and with health problems. In the older old (>75) no correlates of non-response were found (Launer *et al*., 1994). In 2001, data on vital status were obtained from the community registers. This enabled studying the association between generalized anxiety (ANX), depression (DEP), mixed anxiety-depression (ANXDEP) and mortality. The study was approved by the Medical Ethical Committee of the Vrije Universiteit Amsterdam.

The study sample consisted of all subjects at baseline ($n = 4051$); excluding those who had an organic disorder at baseline ($n = 261$) the total number was 3790.

Measures

A 1-h interview, administered during home visits by specially trained and regularly supervised interviewers, was held to gather information on psychiatric symptoms, demographic and medical status. The

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interview consisted of the Dutch translation of the Mini Mental State Examination (Folstein *et al*., 1975), all geriatric Mental State Examination-items related to organic, affective and anxiety syndromes (Copeland *et al*., 1986), the activities of daily living (ADL) scale (Katz *et al*., 1963), the Instrumental Activities of Daily Living (IADL) scale (Lawton and Brody, 1969) and the CAMDEX-interview (Roth *et al*., 1986). GMS-AGECAT generates both syndrome levels (in our study generalized anxiety disorder, depression and organic) and hierarchically defined diagnostic levels, levels represent increasing severity of the disorder, with case level 5 indicating the most severe end of the spectrum. Case levels 1 and 2 are classified as subcases whereas levels 3–5 have been proven valid to detect cases requiring clinical attention in the community (Copeland *et al*., 1986; Copeland *et al*., 1987; Copeland *et al*., 1992). Cognitive status was assessed by MMSE. The interview was administered during home visits by lay interviewers who were specially trained using video sessions and were regularly supervised.

Psychopathology. Diagnoses of ANX, DEP and ANXDEP were made according to the GMS-AGECAT system (Copeland *et al*., 1986, 1988). The syndrome levels of ANX and DEP cases at baseline were defined as AGECAT level 3 or higher. If subjects had both diagnoses they were classified as ANXDEP, defined as both level three on generalized anxiety and depression.

Demographic variables, environmental variables and physical health. Potentially confounding sociodemographic factors were sex, age and level of education. Educational status was dichotomized in lower (primary school or less) and higher (more than primary school) education. Environmental vulnerability factors were marital status and social support. Social support was ascertained by the question: 'Do you get help from your children, neighbours or other acquaintances?' Physical health variables were cardiovascular and cerebrovascular disease, cancer, lung disease, diabetes, Parkinson's disease, arthritis, epilepsy, cognitive status and functional disability. Chronic diseases were assessed with the CAMDEX questions on these diseases. Cognitive status was assessed by MMSE score. Subjects were considered to have functional disability if their ADL or IADL scores were two or more points below the maximum score on the respective scales.

Mortality. The follow-up for recording deaths extended from baseline until the first of January 2001, a follow-up period of 10 years with an average follow-up of 117.8 months, ranging from 109.2–127.2 months. The dates of death were ascertained through the registers of the municipality of Amsterdam or the municipalities where subjects had moved during the study period.

Data analysis

Baseline sample characteristics are compared between men and women (Table 1). Differences between men and women were calculated using chi-square statistics.

Bivariate associations. First odds ratio's using chi square statistics [95% Confidence Intervals (CI)] were calculated for all risk factors potentially associated with mortality in the whole sample and for men and women separately (Table 2). A Kaplan-Meyer curve was further used to examine the association between ANX, DEP, ANXDEP and mortality (Figure 1).

Multivariate associations. Cox proportional hazard regression models (Table 3) were used to further examine the association between ANX, DEP, ANXDEP and mortality. The effect of ANX, DEP and ANXDEP on mortality was studied with successive adjustment for potential confounding factors (demographic variables, environmental variables and physical health) and for men and women separately. Sex differences were tested by adding the interacting term intersex (depression $\times$ sex) to the model.

RESULTS

Sample characteristics

The overall prevalences of ANX, DEP and ANXDEP were 3.2%, 12.9% and 1.9% respectively. The total prevalence of ANX was found to be 2.8 times higher in women than in men. For DEP this was 2.2 times higher in women, for ANXDEP this was 5.4 times. In bivariate analysis, men and women differed on most disease variables. Men had more myocardial infarction, lung disease and Parkinson's disease; women had more arthritis and diabetes. Functional disabilities were more common in women. The majority of men were married, whereas the majority of women were not married. More women than men had ANX, DEP

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Table 1. Baseline sample characteristics for men and women

Variables	All (n, %)	Men (n, %)	Women (n, %)	Statistics (Chisq/df/p)
N	4051	1523	2528	
Organic				ns
	261 (6.4)	85 (5.6)	176 (7.0)	
ANX				35.5/1/***
	128 (3.2)	16 (1.1)	112 (4.4)	
DEP				78.6/1/***
	523 (12.9)	105 (6.9)	418 (16.5)	
ANXDEP				26.6/1/***
	76 (1.9%)	7 (0.5%)	69 (2.7)	
Age				23.3/3/***
65–69	836 (20.6)	350 (23.0)	486 (19.2)	
70–74	974 (24.0)	396 (26.0)	578 (22.9)	
75–79	1050 (25.9)	389 (25.5)	661 (26.1)	
80–86	1191 (29.4)	388 (25.5)	803 (31.8)	
Education				79.9/1/***
>primary school	2335 (57.6)	1014 (66.6)	1321 (52.3)	
Primary school or <	1716 (42.4)	509 (33.4)	1207 (47.7)	
Myocardial infarction				53.7/1/***
	416 (10.3)	225 (14.8)	191 (7.6)	
Stroke				ns
	230 (5.7)	95 (6.2)	135 (5.3)	
Cancer				ns
	449 (11.1)	154 (10.1)	295 (11.7)	
Lung disease				26.5/1/***
	663 (16.4)	308 (20.2)	355 (14.0)	
Arthritis				99.6/1/***
	694 (17.1)	145 (9,5)	549 (21.7)	
Diabetes				3.9/1/*
	360 (8.9)	118 (7.7)	242 (9.6)	
Epilepsy				ns
	70 (1.7)	26 (1.7)	44 (1.7)	
Parkinson				4.5/1/*
	59 (1,5)	30 (2.0)	29 (1.1)	
MMSE				12.1/2/**
26–30	3281 (81.0)	1274 (83.7)	2007 (79.4)	
22–25	522 (12.9)	163 (10.7)	359 (14.2)	
0–21	248 (6.1)	86 (5.6)	162 (6.4)	
ADL disability				10.5/1/**
	325 (8.0)	95 (6.2)	230 (9.1)	
IADL disability				33.2/1/***
	1039 (25.6)	313 (20.6)	726 (28.7)	
Marital status (y)				559.4/1/***
	1970 (48.7)	1105 (72.6)	865 (34.2)	
Social support (y)				58.4/1/***
	842 (20.8)	221 (14.5)	621 (24.6)	

Chi-square test for differences between men and women, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, ns = not significant; $p > 0.05$.

and ANXDEP [(35.4/1/.000, 78.6/1/.000 and 26.6/1/.000 (Chi-square/df/p), Table 1)].

Associations of risk factors with mortality

At follow-up after ten years, 2095 (51.7%) subjects had died during the study period: 60.2% of the men and 46.6% of the women.

Bivariate analysis of baseline characteristics (deceased or alive on 1 January 2001), showed that all risk factors, except ANX (in both sexes), ANXDEP (in both sexes), arthritis (in women) and epilepsy (in both sexes), were associated with excess mortality (Table 2), 51.4% (66.7% of men and 48.1% of women) of subjects with ANX had died at follow up. In DEP this was 56.8% (80.8% of men and 49.7% of women). In ANXDEP this was 50.7 (66.7 for men and 47.8 for women).

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Table 2. Bivariate associations of risk factors with mortality in the full sample and in men and women seperately

Mortality	All%	OR	Men%	OR	Woman%	OR
ALL	50.0	(N = 1873)	58.9	(N = 840)	44.5	(N = 1033)
ANX	52.3	1.15 (0.63–2.08)	75.0	2.23 (0.49–11.07)	47.2	1.19 (0.61–2.30)
DEP	59.0	**1.51** (1.22–1.87)	81.7	**3.31** (1.87–5.86)	52.9	**1.49** (1.17–1.90)
ANXDEP	50.7	1.08 (0.66–1.75)	66.7	1.48 (0.27–8.13)	49.2	1.29 (0.77–2.14)
Age						
65–69	28.1	0.31 (0.26–0.37)	37.8	0.32 (0.25–0.41)	21.1	0.26 (0.21–0.34)
70–74	37.0	0.50 (0.43–0.58)	44.9	0.46 (0.36–0.58)	31.6	0.49 (0.40–0.60)
75–79	55.6	1.36 (1.17–1.57)	68.1	1.68 (1.31–2.17)	48.4	1.24 (1.03–1.49)
80–86	73.2	3.91 (3.34–4.58)	85.6	5.85 (4.24–8.08)	67.0	3.77 (3.12–4.55)
Education						
>Primary school	46.3	**1.44** (1.26–1.64)	54.7	**1.77** (1.40–2.24)	39.9	**1.50** (1.28–1.77)
Primary school or <	55.4		68.1		50.0	
Myocardial infarction	47.9	**2.34** (1.87–2.94)	57.1	**1.73** (1.26–2.37)	42.7	**2.68** (1.94–3.72)
(no/yes)	68.3		69.7		66.7	
Stroke	49.0	**2.23** (1.65–3.02)	57.8	**2.37** (1.42–3.96)	43.6	**2.12** (1.44–3.11)
(no/yes)	68.2		76.5		62.1	
Cancer	49.1	**1.39** (1.13–1.71)	57.9	**1.57** (1.08–2.27)	43.6	**1.37** (1.07–1.77)
(no/yes)	57.2		68.3		51.5	
Lung disease	48.0	**1.64** (1.37–1.95)	56.3	**1.78** (1.35–2.35)	43.3	**1.41** (1.11–1.78)
(no/yes)	60.2		69.6		51.9	
Arthritis	49.6	1.09 (0.92–1.29)	58.1	**1.48** (1.01–2.15)	43.6	1.18 (0.97–1.44)
(no/yes)	51.8		67.2		47.7	
Diabetes	48.3	**2.19** (1.72–2.78)	57.6	**2.21** (1.42–3.44)	42.6	**2.31** (1.73–3.09)
(no/yes)	67.2		75.0		63.1	
Epilepsy	49.8	1.63 (0.94–2.82)	58.8	1.52 (0.57–4.01)	44.3	1.76 (0.90–3.43)
(no/yes)	61.8		68.4		58.3	
Parkinson	49.5	**6.86** (3.09–15.22)	58.4	**5.71** (1.71–19.04)	44.0	**7.31** (2.52–21.20)
(no/yes)	87.0		88.9		85.2	
MMSE						
26–30	47.0	**0.43** (0.35–0.52)	56.5	**0.40** (0.28–0.58)	40.9	**0.40** (0.32–0.51)
22–25	64.7	**2.00** (1.63–2.44)	74.7	**2.20** (1.49–3.25)	60.2	**2.09** (1.64–2.66)
0–21	82.6	**4.88** (2.79–8.55)	84.4	**3.85** (1.47–10.05)	81.5	**5.69** (2.85–11.35)
ADL disability	48.2	**3.26** (2.44–4.37)	57.2	**12.18** (4.41–33.63)	42.5	**2.89** (2.10–3.99)
(no/yes)	75.2		94.2		68.1	
IADL disability	42.9	**3.88** (3.27–4.60)	53.8	**4.23** (2.98–6.00)	35.4	**4.43** (3.62–5.42)
(no/yes)	74.4		83.1		70.8	
Marital status	46.9	**1.28** (1.12–1.45)	55.1	**1.87** (1.45–2.40)	36.2	**1.68** (1.42–2.01)
(yes/no)	53.0		69.6		48.9	
Social support	46.2	**2.20** (1.86–2.60)	56.0	**2.72** (1.91–3.87)	39.4	**2.40** (1.97–2.93)
(no/yes)	65.4		77.6		61.0	

Deceased or alive on 1 January 2001.
% deceased of baseline category, odds ratio with 95% confidence interval, *reference category, significant OR bold.

In Kaplan-Meyer analysis, ANX was found to have no association with excess mortality; no difference was found between men and women. Also ANXDEP was not associated with excess mortality whereas DEP showed an effect on mortality. The effect of depression was more pronounced in men [(Kaplan Meyer survival plot, log rank test: ANX .00/1/.99, DEP15.76/1/0.0001, ANXDEP .00/1/0.95 (Chi sq/df/p)].

In stepwise hierarchical regression using the Cox proportional hazards model with adjustment for potential confounding and explanatory variables both ANX and ANXDEP were not associated with survival. The unadjusted hazard ratio for ANX was 1.02 (0.67–1.54) for all, 1.29(0.58–2.88) for men and 1.08 (0.67–1.74) for women. In ANXDEP this was 1.05 (0.74–1.47) for all, 1.39(0.52–3.72) for men and 1.19(0.83–1.72) for women. In DEP this was 1.36(1.19–1.56) for all, 2.35(1.83–3.02) for men and 1.33(1.13–1.58) for women yielding a significant difference between the sexes in DEP. Sex difference in DEP was statistically significant ($p < 0.001$ unadjusted) and 0.05 (adjusted). In women DEP lost significance after adjustment for the different variables (results DEP shown in Table 3).

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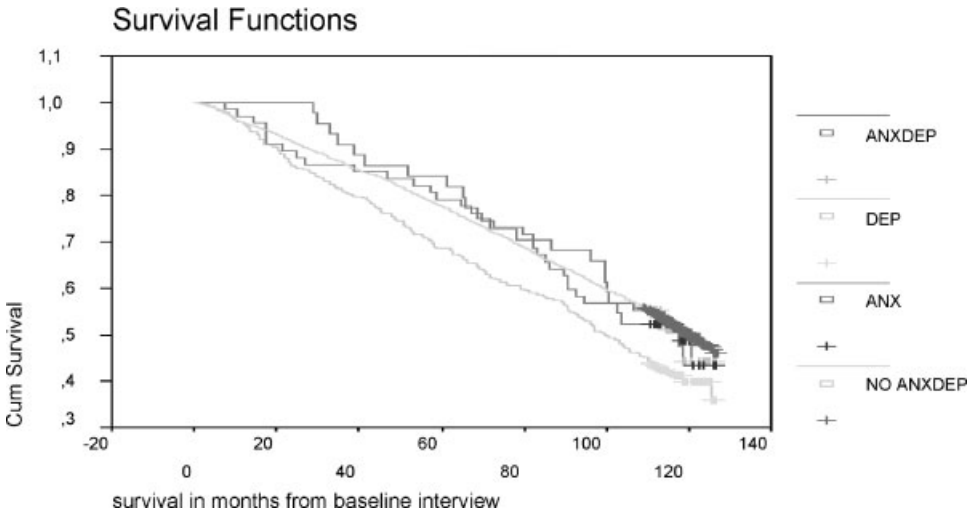

Figure 1. Kaplan-Meyer survival curve for generalized anxiety disorder, mixed generalized anxiety-depression and depression

DISCUSSION

This study was performed to establish the relationship between generalized anxiety disorder, depression and mixed anxiety-depression and excess mortality in older persons living in the community. Due to the large sample size, the long follow up period and the incorporation of a wide range of other risk factors influencing mortality, this study was suitable to perform this task. Attention was paid to gender differences based on earlier investigations showing differential associations in men and women.

Main findings

The overall prevalence of generalized anxiety disorder was 3.2%. This is in line with prevalences found in earlier studies in community living elderly (Flint, 2005). Similarly, the overall prevalence of depression (12.9%) was in line with what has been found in other studies of depression in community-living elderly (Beekman *et al*., 1999). 1.9% in our study had both ANX and DEP.

Also in line with the literature (Beekman *et al*., 1998; Schoevers *et al*., 2000) prevalences in women were significantly higher than those in men. In depression, a large proportion of depressed men had died after ten years follow-up whereas in women this proportion was clearly lower but still considerable. In generalized anxiety and mixed anxiety depression there was no significant excess mortality compared with subjects without generalized anxiety and mixed anxiety-depression.

The unadjusted odds ratios showed generalized anxiety and mixed anxiety–depression not to influence

Table 3. Hazard ratios for depression in the full sample and in men and women seperately with successive adjustment for potential confounders and explanatory variables

Depression *vs* none (n *vs* n)			
Hazard ratio	All (455 *vs* 3291)	Men (88 *vs* 1337)	Women (367 *vs* 1954)
Unadjusted ratio	**1.36** (1.19–1.56)	**2.35** (1.83–3.02)	**1.34** (1.13–1.58)
Adjustment for:			
Age/education	**1.27** (1.10–1.46)	**2.26** (1.76–2.91)	**1.28** (1.08–1.51)
Myocardial infarction/stroke	**1.26** (1.10–1.45)	**2.07** (1.61–2.68)	**1.29** (1.09–1.52)
Other diseases	**1.18** (1.02–1.36)	**1.79** (1.38–2.33)	**1.20** (1.007–1.42)
MMSE	1.14 (0.99–1.31)	**1.77** (1.36–2.30)	1.16 (0.97–1.37)
ADL, IADL disability	1.03 (0.89–1.19)	**1.51** (1.15–1.97)	1.04 (0.87–1.24)
Marital status/Social support	1.05 (0.90–1.21)	**1.44** (1.09–1.89)	1.04 (0.87–1.24)

Cox proportional hazards model, 95% C.I., results generalized anxiety *vs* none and depression-generalized anxiety *vs* none are reported in text; significant HR bold.

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mortality. After controlling for explanatory variables, this finding did not change. Generalized anxiety and mixed anxiety depression were not associated with excess mortality. The finding that (generalized) anxiety is not associated with mortality is consistent with earlier findings showing that generalized anxiety is not associated with a higher mortality risk (Murphy *et al*., 1987).

Other studies found an increased mortality risk for anxiety disorders in men but not in women (Van Hout *et al*., 2004). However, in this study the mortality risk was ascertained for all anxiety disorders whereas in our study specific generalized anxiety was investigated. Especially panic disorder has been shown to be associated with high mortality rates in men due to cardiovascular and cerebrovascular events (Weissman *et al*., 1990). Also, phobic anxiety has been shown to be associated with an increased cardiac risk in some populations (Haines *et al*., 1987). Possibly these different findings in literature may be explained by the differences in anxiety populations.

In depression, the unadjusted odds ratio was associated with mortality in both men and women. This is consistent with our earlier findings (Schoevers *et al*., 2000). Depression in women did not predict mortality when adjusted for other variables related to mortality.

In the current study generalized anxiety and mixed anxiety – depression are not associated with excess mortality. Our data show that generalized anxiety possibly has a protective effect on mortality in depressed elderly whereas depression is associated *with a higher mortality risk in men.*

Methodological considerations

Limitations. A first limitation is that numbers of cases were relatively small compared with control cases, especially in men with generalized anxiety and mixed anxiety-depression. Earlier data have also shown that anxiety disorders (and generalized anxiety) in men are less prevalent than in women (Beekman *et al*., 1998).

Second: selection bias may have affected the validity of the study population because elderly persons living in institutions were excluded. Ethnic minority groups and immigration populations may be underrepresented because people not sufficiently able to speak Dutch to understand the questions of the GMS-AGECAT interview were excluded. Generalization to rural populations may also be difficult as our sample is of people living in the city of Amsterdam. In the Netherlands rural populations generally have lower levels of psychopathology (Peen and Dekker, 2004).

Finally with our data it is difficult to disentangle cause and effect. We did not study the mechanisms responsible for the association between psychopathology and mortality; also we were not able to study causes of death. Even though a relatively large number of potential predictors of mortality were investigated in multivariate analyses, it remains possible that certain confounders were not identified.

Strengths. The strength of our study is a long follow-up period with diagnoses on generalized anxiety, depression and mixed anxiety-depression in a large general population sample with largely complete mortality data.

Explanations

Generalized anxiety has been suggested to have a positive influence on patients' illness behaviour. Evidence has also shown that nonphobic anxiety will get patients to see their doctors more frequently. Furthermore, anxious patients may be more inclined to receive additional examinations, for example they are more likely to receive coronary angiography even in the presence of less severe or insignificant coronary disease. This could facilitate earlier diagnosis and initiation of adequate treatment and counteract the effect of depression (Schocken *et al*., 1987; Hermann *et al*., 2000).

In contrast, panic disorder is associated with more suicidal ideations and suicide attempts and its risk of suicide attempts is found to be comparable with that in major depression (Weissman *et al*., 1989; Johnson *et al*., 1990). Moreover there is evidence of an association between panic disorder and cardiovascular/cerebrovascular events (Weissman *et al*., 1990).

With respect to depression it has long been pointed out that untreated depressed subjects tend to be worse in health and are more likely to die from accidents or suicide (Malzberg, 1937; Tsuang *et al*., 1978; Cuijpers and Smit, 2002). In addition, depression may have adverse effects on endocrine, neurologic and immune processes and may interfere with the patient's motivation toward recovery and compliance with treatment (Cuijpers and Smit, 2002; Cuijpers and Schoevers, 2004). Furthermore, depression may act on mortality through multiple relatively independent pathways, which pathways may lead to double feedback loops. For example: depression is known to increase the likelihood of functional impairment, and functional impairment in turn, is a risk factor for depression (Penninx *et al*., 2000; Blazer *et al*., 2001).

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Implications

Earlier research suggested that the whole cluster of anxiety disorders, like depression, is associated with excess mortality in older persons. To our knowledge, this is the first study in the elderly in a general population that especially investigated generalized anxiety disorder in relation to mortality, and this did not yield such an association. If replicated, our findings suggest that generalized anxiety may influence the course of depression but not mortality. A possible explanation is that patients seek help in an earlier stage. However, different neurobiological mechanisms in generalized anxiety and depression may also explain this possible difference. Generalized anxiety should therefore be distinguished from other anxiety disorders and depression when studying mortality risk.

In contrast, generalised anxiety was also found to be associated with both depression severity and an untoward course of depression (Schoevers *et al*., 2005). It is intriguing that generalized anxiety thus appears to have a differential effect on different depression outcome parameters. The nature of this pattern remains to be elucidated.

The next steps for research would be to further investigate:

1. the role of generalized anxiety and other anxiety disorders in their effect on survival;
2. the mechanisms behind the possibly different pathophysiology of depression and (generalized) anxiety in relation to survival; and
3. the possible differences in help seeking behaviour in patients with depression and generalised anxiety disorder.

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